

**In the claims:**

All claims being examined, whether or not amended, are presented below.

46. (Canceled)

47. (Allowed - Amended) A method for identifying an agent that inhibits an interaction of EphrinB2 and EphB4, comprising:

(a) combining:

- (1) an EphrinB2 protein or at least a portion thereof sufficient to interact with an EphB4 protein,
- (2) ~~the~~ an EphB4 protein or at least a portion thereof sufficient to interact with said EphrinB2 protein, and
- (3) an agent,

under conditions appropriate for interaction between said EphrinB2 and EphB4 proteins in the absence of said agent;

- (b) determining the extent to which said EphrinB2 and EphB4 proteins interact;
- (c) comparing the extent of interaction determined in (b) with the extent to which interaction of said EphrinB2 and EphB4 proteins occurs in the absence of the agent;

wherein if the extent ~~to which~~ of the interaction of said EphrinB2 and EphB4 proteins is less in the presence of the agent than in the absence of the agent, the agent is one which inhibits interaction of EphrinB2 and EphB4; and

- (d) for an agent that inhibits said interaction, further assessing the ability of said agent to interfere with blood vessel formation.

49. (Canceled)

50. (Allowed - Amended) A method for identifying an agent that enhances an interaction of EphrinB2 and EphB4, comprising:

- (a) combining:
    - (1) an EphrinB2 protein or at least a portion thereof sufficient to interact with an EphB4 protein,
    - (2) ~~the~~ an EphB4 or at least a portion thereof sufficient to interact with said EphrinB2 protein, and
    - (3) an agent,under conditions appropriate for interaction between said EphrinB2 and EphB4 proteins in the presence of said agent;
  - (b) determining the extent to which said EphrinB2 and EphB4 proteins interact;
  - (c) comparing the extent of interaction determined in (b) with the extent to which interaction of said EphrinB2 and EphB4 proteins occurs in the absence of the agent;
- wherein if the extent ~~to which~~ of the interaction of said EphrinB2 and EphB4 proteins is greater in the presence of the agent than in the absence of the agent, the agent is one which enhances interaction of EphrinB2 and EphB4; and
- (d) for an agent that enhances said interaction, further assessing the ability of said agent to enhance blood vessel formation.

77. – 86. (Canceled)

- 88. (Allowed - Amended) The method of Claim 47, 50 or 151, wherein the extent of the interaction between said EphrinB2 and EphB4 proteins is determined by detecting binding of the EphrinB2 and EphB4 proteins, wherein at least one of said EphrinB2 and EphB4 proteins includes a detectable label.
- 89. (Allowed) The method of Claim 88 wherein the label is selected from the group consisting of a radioactive label, a fluorescent label and a colorimetric label.
- 92. (Allowed) The method of Claim 47, 50 or 151, wherein

- (a) the EphrinB2 protein is expressed on a cell; and/or
  - (b) the EphB4 protein is expressed on a cell.
93. **(Allowed)** The method of Claim 92, wherein
- (a) the EphrinB2 protein is expressed on an isolated arterial endothelial cell; and/or
  - (b) the EphB4 protein is expressed on an isolated venous endothelial cell.
95. **(Allowed)** The method of Claim 92, wherein
- (a) the EphrinB2 protein is expressed on a cell which has been genetically modified to recombinantly express the EphrinB2 protein,
  - (b) the EphB4 protein is expressed on a cell which has been genetically modified to recombinantly express the EphB4 protein; or
  - (c) both (a) and (b).
96. **(Allowed)** The method of Claim 47, 50 or 151, wherein
- (a) the EphrinB2 protein is conjugated to a solid support and the EphB4 protein is diffusible; or
  - (b) the EphB4 protein is conjugated to a solid support and the EphrinB2 protein is diffusible.
97. **(Allowed)** The method of Claim 96 wherein the solid support in (a) or (b) is selected from the group consisting of a bead, column pore glass, a pin and the wall of a plate.
98. **(Allowed)** The method of Claim 47, 50 or 151, wherein at least one of said EphrinB2 protein and EphB4 protein is a fusion protein.
99. **(Allowed)** The method of Claim 98 wherein the fusion protein includes an Fc domain.
100. **(Allowed)** The method of Claim 98 wherein the fusion protein is soluble.

107. **(Allowed)** The method of Claim 47, 50 or 151, wherein
- (a) the EphrinB2 protein is expressed on a cell; and
  - (b) the EphB4 protein is a soluble protein including an extracellular fragment of EphB4 which binds to the EphrinB2 protein.
108. **(Allowed-Amended)** The method of Claim 47, 50 or 151, wherein
- (a) the EphrinB2 protein is a soluble protein including an extracellular fragment of EphrinB2 which binds to the EphB4 protein ; and
  - (b) the EphB4 protein is expressed on a cell ~~which is contacted with said EphrinB2 protein and agent.~~
114. **(Canceled)**
120. **(Canceled)**
151. **(Allowed - Amended)** A method for ~~identify~~ identifying an agent having an anti-angiogenic activity, comprising
- (a) combining
    - an EphrinB2 protein, or a portion thereof that interacts with EphB4, and
    - an EphB4 protein, or a portion thereof that interacts with EphrinB2,wherein said EphrinB2 and EphB4 proteins interact to form a ligand-receptor complex;
  - (b) determining if a test agent can interfere with a function of said ligand-receptor complex; and

- (c) for said test agent that interferes with said ligand-receptor complex, administering said agent to a nonhuman animal and measuring the anti-angiogenic activity, if any, of said agent.
152. **(Allowed)** The method of Claim 47, 50 or 151, wherein at least one of the EphrinB2 protein and EphB4 protein are expressed on cultured cells, and the agent is added to culture medium in which the cells are placed.
153. – 155. **(Canceled)**
156. **(Allowed - Amended)** A method for ~~identify~~ identifying an agent having an anti-angiogenic activity comprising:
- (a) contacting
    - (i) cells expressing an EphB4 protein, which cells differentiate or maintain a venous phenotype in a manner dependent on the activity of the EphB4 protein, and
    - (ii) a test agent; and
  - (b) determining if the agent can interfere with the ability of said EphB4 protein to transduce a signal that affects said venous phenotype; ~~and~~
  - ~~(c) administering, to a nonhuman animal, an agent identified in (b), and measuring the anti-angiogenic activity, if any, of said agent.~~
157. **(Allowed - Amended)** A method for ~~identify~~ identifying an agent having an anti-angiogenic activity comprising:
- (a) contacting

- (i) cells expressing an EphrinB2 protein, which cells differentiate or maintain an arterial phenotype in a manner dependent on the activity of the EphrinB2 protein, and
    - (ii) a test agent; and
  - (b) determining if the agent can interfere with the ability of said EphrinB2 protein to transduce a signal that affects said arterial phenotype; ~~and~~
  - ~~(c) administering, to a nonhuman animal, an agent identified in (b), and measuring the anti-angiogenic activity, if any, of said agent.~~
158. **(New)** The method of claim 156, wherein the cells expressing an EphB4 protein are selected from the group consisting of: venous endothelial cells and cells of a cell line derived from venous endothelial cells.
159. **(New)** The method of claim 157, wherein the cells expressing an EphrinB2 protein are selected from the group consisting of: arterial endothelial cells and cells of a cell line derived from arterial endothelial cells.
160. **(New)** A method for evaluating the effect of an agent on angiogenesis comprising:
- (a) identifying or obtaining an agent that exhibits one or more of the following properties:
    - (i) interferes with the ability of an EphB4 protein to transduce a signal that affects a venous phenotype of an endothelial cell;
    - (ii) interferes with the ability of an EphrinB2 protein to transduce a signal that affects an arterial phenotype of an endothelial cell;
    - (iii) decreases the extent of interaction between an EphB4 polypeptide and an EphrinB2 polypeptide; and
  - (b) evaluating the effect of said agent on angiogenesis in a non-human animal.

161. **(New)** A method of claim 160, wherein evaluating the effect of said agent on angiogenesis in a non-human animal comprises: implanting tumor cells in the non-human animal and evaluating the effect of said agent on arterial vessel growth into the resultant tumor.
162. **(New)** A method of claim 160, wherein evaluating the effect of said agent on angiogenesis in a non-human animal comprises: evaluating the effect of said agent on ischemia-associated neovascularization.
163. **(New)** A method of claim 162, wherein the ischemia-associated neovascularization is cardiac neovascularization.